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Relationship between serum vitamin D levels and Parkinson's disease staging: a clinical observational study

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ABSTRACT

Background and Objectives. After Alzheimer's, Parkinson's disease ranks second most common neurodegenerative disease; recent research has linked neurodegenerative diseases to vitamin D levels. By means of neurotrophic factors controlling neuron development and preventing cytotoxicity, vitamin D is supposed to have neuroprotective effects. According to some studies, higher serum vitamin D levels correlate with a lower stage of Parkinson's disease as measured on the Hoehn and Yahr scale. Still, studies on South Asia especially in Indonesia are few. The aim of this paper is to investigate the relationship between the stages of Parkinson's disease and serum vitamin D levels.

Materials and Methods. This work uses a cross-sectional analytical observational design. Samples were gathered from members of the Bali Parkinson's Community, Parkinson's patients under treatment at the Neurology Clinic of Prof. Dr. I.G.N.G. Ngoerah General Hospital, and patients unable to make it to the clinic by home visits. A neurologist validated the Parkinson's disease diagnosis; disease stages were assessed with the modified Hoehn and Yahr scale; serum vitamin D levels were measured using the international scale (deficiency defined as <30 ng/ml).

Results. Sixty subjects were involved, with a male dominance (61.7%) and an average age of 59 ± 10.476 years. Parkinson's disease stages consisted of stage 1 (5%), stage 1.5 (11.7%), stage 2 (13.3%), stage 2.5 (6.7%), stage 3 (16.7%), stage 4 (23.3%), and stage 5 (23.3%). The median serum vitamin D level was 37.5 ng/ml.

Conclusions. Simple ordinal logistic regression analysis showed an OR of 0.935 and an estimate coefficient (ß) of -0.067, indicating a negative relationship between serum vitamin D levels and Parkinson's disease stage. This result was statistically significant ($p<0.001$), suggesting that higher vitamin D levels are associated with lower stages of Parkinson's disease. Each one-unit increase in serum vitamin D concentration is linked to a 6.5% reduction in the risk of disease progression.

Keywords: Parkinson's Disease, Vitamin D, Hoehn and Yahr modification scale

Abbreviations: PCR, Polymerase Chain Reaction; ELISA; Enzyme-Linked Immunosorbance Assay

INTRODUCTION

Parkinson's disease (PD) is a condition that gets worse over time and affects the brain, mainly marked by lower dopamine levels in certain brain areas, loss of color in the substantia nigra, the presence of Lewy bodies, and damage to nerve cells in the basal ganglia. The link between low vitamin D levels and PD has been the subject of several studies over the last 20 years. However, there is still a dearth of information on the serum vitamin D status of PD patients, especially in South Asian populations like Indonesia.

Numerous studies have reported the clinical distribution of PD stages using the Hoehn and Yahr (H&Y) scale. According to El-Tallawy et al., less than 5% of cases were in stage 5, while 55% of cases were in stages 1 and 2 [1]. According to Larasanti et al., 44.7% of patients in Bali, Indonesia, were in stage 2, 34% were in stage 3, and none were in stage 5. Due to their limited mobility in advanced stages, only 8.5% of patients routinely attended hospital checkups [2]. Similar to Kashihara and Kitayama's findings, a study at Dr. Sardjito General Hospital revealed that 44% of patients were in stages 1-2, 20% were in stage 3, and 20% were in stages 4-5 [3, 4].

The role of vitamin D in the pathogenesis of PD has been widely studied. Low levels of 25(OH)D might lead to the death of dopamine-producing neurons because it lacks protective effects on the brain. Fullard (2020) reported a higher prevalence of vitamin D deficiency in PD patients than in healthy controls. Researchers found that both the vitamin D receptor (VDR) and the enzyme 1α-hydroxylase, which changes vitamin D into its active form, are found in high amounts in the substantia nigra, leading to the idea that low vitamin D levels might cause problems or death of neurons in this area [5].

Other studies have shown an inverse relationship between higher Unified Parkinson's Disease Rating Scale (UPDRS) scores and H&Y stage and lower 25(OH)D3 and total 25(OH)D levels. These studies concluded that decreased vitamin D concentrations were associated with greater disease severity, although not with disease duration or patient age. The DATATOP study confirmed that 25(OH)D levels do not decline during PD progression. Suzuki et al. found that patients who took vitamin D supplements had a slower progression of PD, as measured by the H&Y scale and their daily activities, and they reported a better quality of life according to the Parkinson's Disease Questionnaire (PDQ-39). In contrast, the placebo group exhibited more rapid disease progression, as evidenced by higher UPDRS-III scores. Sleeman et al. found that lower baseline serum 25(OH)D levels were associated with more severe PD progression based on UPDRS-III, while Moghaddasi et al. linked low 25(OH)D levels with postural instability, freezing of gait, and postural abnormalities [6, 7, 8, 9, 10, 11, 12].

Diet and skin synthesis after exposure to ultraviolet B (UVB; 290–315 nm) radiation are the two main sources of vitamin D (25-hydroxyvitamin D). Consequently, vitamin D deficiency may result from inadequate sun exposure. Numerous tissues, such as the kidneys, bones, intestines, muscles, pancreas, and central nervous system, exhibit widespread expression of the VDR [12]. By controlling neurotrophic factors, neuronal growth, and providing defense against cytotoxicity, vitamin D may have neuroprotective effects. Several studies found that $1,25(OH)_2D_3$ boosted the

production of neurotrophins, like neurotrophin-3 (NT-3) and glial cell line-derived neurotrophic factor (GDNF). In rodent models, Riaz et al. and Wang et al. showed a correlation between neurotrophin stimulation induced by vitamin D and neuroprotective effects. Vitamin D_2 supplementation significantly increased axonal diameter and promoted axonal growth in models of peripheral nerve injury [5, 13, 14].

Numerous studies have explored whether reduced serum 25(OH)D levels are a risk factor for PD, defining deficiency as <50 nmol/L and insufficiency as <75 nmol/L [15, 5]. A previous study suggested that sunlight exposure (>15 minutes/week) reduces PD risk, and it has been hypothesized that persistent vitamin D insufficiency may play a role in neurodegenerative disease pathogenesis, particularly PD [11].

According to Hu et al., exposure to outdoor sunlight for more than five hours per day during the summer was linked to a 16% lower risk of PD than exposure for less than two hours per day. In winter, exposure of more than two hours per day was linked to a 15% lower risk than exposure of less than one hour per day. An annual risk reduction of 15% was associated with an average of more than 3.5 hours of sunlight per day, rather than less than 1.5 hours [16].

No disease-modifying treatment (DMT) has been proven to change the progression of PD to date. Vitamin D may be used as a possible adjunctive therapy to alleviate symptoms and slow the progression of the disease because of its neuroprotective qualities (Fullard et al., 2020). This study intends to examine the relationship between serum vitamin D levels and Parkinson's disease stage, given the paucity of research on serum vitamin D status among PD patients in Indonesia.

MATERIALS AND METHODS

Samples and ethical clearance

This study adopts an analytical observational design with a cross-sectional approach to examine the correlation between serum vitamin D levels and disease staging in individuals with Parkinson's disease. We contacted members of the Bali Parkinson Community via telephone and, with their consent, conduct assessments at the same hospital. For those unable to attend in person, home visits were arranged. Eligibility criteria include individuals diagnosed with Parkinson's disease by a neurologist, currently receiving dopaminergic therapy, aged 30 to 70 years, receiving treatment at the designated clinic, and affiliated with the Bali Parkinson Community. Participation requires informed consent. Subjects will not be allowed to participate if they have serious kidney or liver problems, have had a stroke, epilepsy, brain tumors, infections in the brain or spinal cord, autoimmune diseases, or major head injuries, or if they take certain medications that affect how vitamin D works in the body, such as phenytoin, phenobarbital, carbamazepine, or cholestyramine. The research take place at the Neurology Outpatient Clinic of Prof. Dr. I.G.N.G. Ngoerah General Hospital, Denpasar.

Serum vitamin D was measured with the Elabscience 25-HVD3 Human ELISA kit (*E-EL-0015*). Participants with Parkinson's disease who meet the inclusion and exclusion criteria and provide written informed consent asked to complete a data collection form. A neurological motor function examination conducted in the neurology outpatient clinic, assessing gait, postural instability, tremor, muscle strength, tone, and trophic condition. Based on the results, subjects were classified into stages 1–5 according to the Hoehn and Yahr scale by the attending neurologist. Following clinical assessment, serum vitamin D levels were measured. Venous blood samples (5 mL) drawn from the median cubital vein while the patient is in a supine position, using a 5 mL syringe.

Statistical analysis

Data analysis conducted using IBM SPSS Statistics® version 20. Descriptive statistics described the baseline characteristics of study subjects in each group. The Pearson orrelation analysis evaluates the relationship between serum vitamin D levels and disease stage in Parkinson's patients. A simple ordinal logistic regression was utilised to examine the relationship of serum vitamin D level and the stage of Parkinson's disease. The p-value < 0.05 was used to determine a statistically significant analysis.

RESULTS

The study involved 74 subjects; however, 14 subjects with extreme abnormal serum vitamin D values were excluded and grouped according to the modified Hoehn and Yahr disease stage if they met the eligibility criteria. A total of 60 subjects fulfilled the eligibility criteria. The baseline characteristics of the subjects presented in this study include age, gender, education, occupation, stage of Parkinson's disease, duration of Parkinson's treatment, and duration of sun exposure. Variables are summarized on a categorical scale and presented in the form of number (n) and percentage (%).

Table 1 shows that the research subjects' average age was 59 ± 10.476. A total of 37 (61.7%) male subjects and 23 (38.0%) female subjects were included. Four (6.7%) of the research participants had completed elementary school, eight (13.3%) had completed junior high school, twenty-five (41.7%) had completed senior high school, and twenty-three (38.0%) had earned a diploma or higher. The subjects in this study are roughly 59 years old on average.

The subjects are distributed as follows by occupation: 21 individuals are unemployed or retired (35%), 5 individuals are farmers or laborers (8.3%), 4 individuals are self-employed (6.7%), 15 individuals are private employees (25%), and 15 individuals are government employees (25%).

The research participants PD stages were as follows: stage 1, 3 individuals (5%); stage 1.5, 7 individuals (11.7%); stage 2, 8 individuals (13.3%); stage 2.5, 4 individuals (6.7%); stage 3, 10 individuals (16.7%); stage 4, 14 individuals (23.3%); and stage 5, 14 individuals (23.3%).

Nine individuals (15%) had Parkinson's disease for less than a year, 31 individuals (51.7%) had it for one to five years, and 33.3% had it for more than five years. There were 25 participants (41.7%) in the group of subjects exposed to sunlight for less than 30 minutes and 35 participants (58.3%) in the group exposed to sunlight for more than 30 minutes. According to this study, 11 individuals (18.3%) with Parkinson's disease had vitamin D serum deficiency, 11 individuals (18.3%) had insufficiency, and 38 individuals (63.3%) had optimal concentration.

Table 1. General characteristic of subjects

Characteristic of Subjects		n (%)
Gender		
Male		37 (61,7)
Female		23 (38,3)
Age (Years) mean ± SD	59 ± 10,476	
Education		
Elementary School		4 (6,7)
Junior High School		8 (13,3)
Senior High School		25 (41,7)

Diploma or Higher		23 (38,3)
Occupation		
Unemployed or Retired		21 (35)
Farmer or Laborers		5 (8,3)
Self Employed		4 (6,7)
Private Employee		15 (25)
Government Employee		15 (25)
Parkinson Disease Staging		
Stage 1		3 (5)
Stage 1,5		7 (11,7)
Stage 2		8 (13,3)
Stage 2,5		4 (6,7)
Stage 3		10 (16,7)
Stage 4		14 (23,3)
Stage 5		14 (23,3)
Duration of Parkinson Disease		
< 1 Year		9 (15)
1- 5 Years		31 (51,7)
> 5 Years		20 (33,3)
Duration of Sunlight Exposure		
< 30 minutes		25 (41,7)
> 30 minutes		35 (58,3)
Vitamin D Serum (ng/ml):		
Median (IQR)	37,5 (29,73)	
Serum Vitamin D Serum (ng/ml):		
Deficiency (≤20)		11 (18,3)
Insuficiency (21-30)		11 (18,3)
Optimal Concentration (>31-80)		38 (63,3)

Based on Table 2, it was found that all subjects with Parkinson's Disease at modified H&Y stage 1 had optimal Vitamin D concentrations. At stages 1.5 and 3, 37.5% and 20% of subjects, respectively, experienced Vitamin D insufficiency. In stage 4, 21.4% had deficiency, 28.6% had insufficiency, and 50% had optimal concentrations. Meanwhile, in stage 5, 57.1% had deficiency, 14.3% had insufficiency, and 28.6% had optimal concentrations.

Table 2 Profile of Parkinson's Disease Patients Based on Serum Vitamin D Levels

Parkinson Disease Staging	**Concentration 25(OH)D (ng/ml) n (%)**			**Gender**	
	Deficiency (≤ 20)	**Insuficiency (21-30)**	**Optimal Concentration (31-80)**	**Male**	**Female**
Stage 1	-	-	3 (100%)	3 (100%)	-
Stage 1,5	-	-	7 (100%)	2 (28,6%)	5 (71,4%)
Stage 2	-	3 (37,5%)	5 (62,5%)	4 (50%)	4 (50%)

Stage 2,5	-	-	4 (100%)	2 (50%)	2 (50%)
Stage 3	-	2 (20%)	8 (80%)	7 (70%)	3 (30%)
Stage 4	3 (21,4%)	4 (28,6%)	7 (50%)	11 (78,6%)	3 (21,4%)
Stage 5	8 (57,1%)	2 (14,3%)	4 (28,6%)	8 (51,7%)	6 (42,9%)

Normality testing was conducted to assess the distribution of data for variables measured on a numerical scale. In this study, the Kolmogorov-Smirnov test was used due to the sample size of 60 subjects. The variable tested for normality was serum vitamin D levels. The distribution of serum vitamin D levels was not normal, with a p-value < 0.05 based on the Kolmogorov-Smirnov test. The median serum vitamin D level in this study was 37.5, with a minimum value of 13 and a maximum of 75.3. In contrast, age data were normally distributed, with a p-value > 0.05 on the Kolmogorov-Smirnov test, a median of 60, and ranged between 28 to 87 years old.

Correlation Analysis of Serum Vitamin D Levels

Since the distribution of serum vitamin D levels was not normal, Spearman correlation analysis was used. The correlation analysis between serum vitamin D levels and duration of sun exposure yielded an r-value of 0.675 with a p-value < 0.001, indicating a strong and statistically significant positive correlation. This suggests that longer sun exposure duration is associated with higher serum vitamin D levels.

In contrast, the correlation between age and serum vitamin D levels showed an r-value of -0.309 and a p-value of 0.16, indicating no statistically significant correlation (Table 3).

Table 3. Spearman Correlation Analysis of Serum Vitamin D Levels with Age and Duration of Sun Exposure

Variable	**Vitamin D Serum (n=60)**	
	r	**p**
Duration of Sunlight Exposure	0,675	0,000*
Age	-309	0,16

Note: * indicates statistical significance if p < 0.05

The Relationship Between Serum Vitamin D Levels and Parkinson's Disease Stage

Since the distribution of serum vitamin D levels was not normal, Spearman correlation analysis was conducted. The correlation analysis between Parkinson's disease stage and serum vitamin D levels yielded a Spearman correlation coefficient of r = -0.589, indicating a negative correlation of moderate strength that is statistically significant (p < 0.001). The data are presented in Table 4

Table 4 Results of Spearman Correlation Analysis Between Parkinson's Disease Stage and Serum Vitamin D Levels

Variable	**Parkinson Disease Staging**	
	r	**p**
Vitamin D Serum	-0,589	0,000*

Note: * indicates statistical significance at p < 0.05

In this study, since the dependent variable was ordinal and the independent variable was numerical, a simple ordinal logistic regression analysis was conducted to determine the direction of the relationship between the independent and dependent variables. The direction of the relationship was determined based on the estimated coefficient (ß), while the strength of the relationship was measured using the Odds Ratio (OR) with a 95% confidence interval (CI). Statistical significance was set at $p < 0.05$. The results of the simple ordinal logistic regression analysis between serum vitamin D levels and Parkinson's disease stage are presented in Table 5. The analysis showed an estimated coefficient of -0.067, indicating a negative relationship, with a p-value < 0.001, thus demonstrating statistical significance.

Table 5. Simple Ordinal Logistic Regression Analysis of Serum Vitamin D on Parkinson's Disease Stage.

Independent Variable	**Coefisien Estimate (ß)**	**OR**	**CI 95% (lower)**	**CI 95% (Upper)**	***p-value***
Kadar Vitamin D	-0,067	0,935	-0,097	-0,037	0,000*

Note:
*:statistically significant, OR: Odds Ratio; CI: Confidence Interval

In the Model Fitting Information analysis, the -2 Log Likelihood value for the Intercept Only model was 212.355, while for the Final model it was 190.920. The difference between these values resulted in a Chi-Square value of 21.435 with 1 degree of freedom (df), which was statistically significant ($p = 0.000$). This indicates that serum vitamin D levels have a significant effect on the stage of Parkinson's disease.
The Goodness of Fit analysis based on the Pearson test (Chi-Square = 287.429, $p = 0.923$) and the Deviance test (Chi-Square = 183.989, $p = 1.000$), showed that the model did not differ significantly from the observed data. Therefore, the model can be considered reliable in explaining the relationship between serum vitamin D levels and the stage of Parkinson's disease.

Relationship Between Other Variables and Parkinson's Disease Staging

A simple ordinal logistic regression analysis was also performed to examine other variables that may influence Parkinson's disease stage, namely age, gender, and duration of illness. The strength of relationship was measured using the Odds Ratio (OR) with a 95% confidence interval (CI), and statistical significance was determined at $p < 0.05$.
As shown in Table 6, the variable age had an estimated coefficient (β) of 0.124 with a p-value < 0.001 and an OR of 1.132. An odds ratio greater than 1 indicates that for every one-unit increase in age (e.g., one year), the odds of being in a higher stage of Parkinson's disease increase by 13.2%. This result is statistically significant.
For the variable duration of illness, the estimated coefficient (β) was 2.373 with a p-value < 0.001 and an OR of 10.73, suggesting that for each one-year increase in the duration of Parkinson's disease, the odds of being in a more advanced disease stage increase more than tenfold.
In contrast, for the variable gender, the estimated coefficient (β) was -0.344 with a p-value > 0.05 and an OR of 0.709. This indicates no statistically significant relationship between gender and Parkinson's disease stage.

Table 6. Simple Ordinal Logistic Regression of Other Variables on Parkinson's Disease Stage

Independent Variable	Coefficient Estimate (β)	Odds Ratio (OR)	95% CI (Lower)	95% CI (Upper)	*p*-value
Age	0.124	1.132	0.07	0.178	0.000*
Gender	-0.344	0.709	-1.264	0.575	0.463
Duration of PD (years)	2.373	10.73	1.493	3.252	0.000*

Note: *:statistically significant, OR: Odds Ratio; CI: Confidence Interval

DISCUSSION

Systematic review studies have reported that males are at a higher risk of developing Parkinson's disease (PD). The present study also observed this trend, with the majority of participants being male (n = 37, 61.7%). Larasanti et al., reported a male prevalence of 72.3%, which was higher than that of females at 27.7%. This finding is consistent with other studies showing a male-to-female prevalence ratio of 3:2, with disease onset in females occurring at an older age. The later onset in females is believed to be connected to the protective benefits of estrogen on the nigrostriatal dopaminergic system [17, 2].

Hawkes et al., noted that motor symptoms typically progress within five years following the initial onset of prodromal symptoms. Non-motor symptoms, however, are often overlooked or not initially recognized as being related to PD [18].

Previous studies have shown that the prevalence and incidence of PD increase with age, although it can also be diagnosed in individuals in their late 30s and 40s. The average age of PD onset is approximately 55 years. This aligns with the findings of the current study, in which the mean age of participants was around 59 years. As the global elderly population and life expectancy continue to rise, the number of individuals living with PD is projected to increase by up to 50% by 2030 [17, 19, 20].

The 25-hydroxyvitamin D [25(OH)D] is the biomarker commonly used to assess vitamin D status via blood sampling. Levels between 20 and 30 ng/mL are considered insufficient, while levels below 20 ng/mL indicate deficiency [21, 22]. In this study, 11 subjects (18.3%) had vitamin D deficiency, another 11 (18.3%) had insufficient levels, and 38 (63.3%) had optimal concentrations. These results are consistent with the findings of Meamar et al., who observed that serum vitamin D levels tended to be lower in patients with more advanced H&Y stages [23].

Regarding sunlight exposure, 25 participants (41.7%) reported less than 30 minutes of sun exposure per day, while 35 (58.3%) reported more than 30 minutes. Ultraviolet B (UVB) radiation, within the wavelength range of 280–320 nm, plays a role in cutaneous synthesis of vitamin D3, which is also affected by seasonal variation. However, multiple external factors influence UVB exposure and vitamin D production, including sunscreen use and clothing materials. Fabrics such as silk, nylon, polyester, and wool tend to block UV radiation more effectively than linen or cotton. The color of clothing also contributes to UV radiation penetration. Skin pigmentation further affects vitamin D3 synthesis. Individuals with darker skin have higher melanin content and require longer UV exposure to produce the same amount of vitamin D3 compared to those with lighter skin. As people get older, their skin makes much less vitamin D3; for example, those aged 62–80 produce

about 78% less than those aged 20–30, probably because their skin has less 7-dehydrocholesterol [24].

According to the correlation analysis, there is a strong and statistically significant positive relationship between the length of sun exposure and serum vitamin D levels. The value of $r = 0.675$ with a p-value < 0.001 indicates this relationship. The result indicates that serum vitamin D levels increase with the amount of time spent in the sun. Serum vitamin D levels and sun exposure duration were found to be positively correlated. About 10,000 to 20,000 IU of vitamin D can be produced after 30 minutes of sun exposure. Darker skin types, however, require 20–30 times more time to be exposed to the sun [25, 26].

The role of vitamin D in PD has been widely investigated. Low levels of 25-hydroxyvitamin D [25(OH)D] may contribute to dopaminergic neuronal death, potentially influencing the development of idiopathic PD due to the absence of vitamin D's neuroprotective effects. Vitamin D receptors (VDR) are found in nerve cells of the central nervous system (CNS), as well as in support cells like astrocytes and oligodendrocytes, and in areas such as the substantia nigra, cortex, subcortex, hippocampus, hypothalamus, thalamus, and blood vessel cells. The presence of VDR and 1-alpha-hydroxylase the enzyme that converts 25(OH)D into its active form, 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] in the substantia nigra supports the hypothesis that vitamin D activation also occurs within the CNS. Deficiency in vitamin D concentration may result in dopaminergic neuronal death [11]. A research on mice that lacked VDR showed that giving them vitamin D increased dopamine production, which was linked to more tyrosine hydroxylase (TH) being made because more dopaminergic neurons survived. Additionally, giving vitamin D helped lessen the harmful effects on dopamine caused by 6-hydroxydopamine, while reducing VDR levels led to movement problems in mice [28, 11].

Our results are similar to those of Meamar et al., who did a study looking at the link between serum 25(OH)D3, uric acid levels, and how severe idiopathic Parkinson's disease is. In their study with patients in Iran, the authors found that lower levels of serum 25(OH)D3 were linked to higher scores on the Unified Parkinson's Disease Rating Scale (UPDRS), meaning that higher serum levels of 25(OH)D3 were connected to less severe disease. The highest vitamin D levels were observed in patients at Hoehn and Yahr (H&Y) stages 1–1.5 (mean: 23.9 ng/mL), while the lowest levels were found in patients at H&Y stages 4–5 (mean: 14.5 ng/mL) [23].

Our results match those of Sleeman et al., who found that people with lower levels of serum 25(OH)D had more severe Parkinson's disease, as shown by higher UPDRS-III scores. Similarly, Moghaddasi et al. found that low serum vitamin D levels were associated with severe postural instability, freezing of gait, and postural abnormalities [9, 10].

In a study by Peterson et al., a negative correlation was also found between serum vitamin D levels and the degree of Parkinson's disease severity. They investigated the relationship between vitamin D status and balance control, a common issue in Parkinson's disease. While healthy individuals have symmetrical automatic postural responses, patients with PD often exhibit asymmetrical responses. The study found that lower vitamin D levels were correlated with increased postural asymmetry. These poor postural responses might be caused by weaker muscles and changes in how quickly the body reacts to maintain balance, involving parts of the brain and nervous system that have vitamin D receptors [29].

There is a correlation between other variables and the stage of Parkinson's disease. This study analyzed other variables, including age, gender, and disease duration, to determine their

relationship with the stage of PD. The analysis revealed that duration of sun exposure, age, and duration of PD were significantly associated with PD stage.

Regarding disease duration, a positive correlation was observed between the length of time lived with PD and the disease stage. This is consistent with a study by Kashihara and Kitayama, which found that a longer duration of PD was associated with worsening motor and non-motor symptoms [30].

The pathophysiology of PD is associated with alpha-synuclein pathology, a hallmark of progressive neurodegeneration. Alpha-synuclein has been identified in the brains of individuals with PD even before the premotor phase. Braak and others, as mentioned by Wolters, explained the early stages of PD by looking at where alpha-synuclein pathology appears in the brain. In stages 1–2, alpha-synuclein clumps are found only in the olfactory bulb, the front part of the olfactory system, and lower parts of the brain, including the medulla oblongata and pontine tegmentum. In stages 3–4, the disease spreads to areas like the substantia nigra, ventral tegmental area, nucleus basalis of Meynert, and parts of the brain called the mesencephalon and diencephalon. Stages 5–6 are considered the final stages, with pathological involvement reaching the neocortex. Early motor symptoms are thought to start in stages 4 and 5, after more than half of the dopamine-producing neurons in the substantia nigra have already been lost [31, 32, 17].

With respect to gender and its relationship with the PD stage, the results were not statistically significant. In this study, 11 male subjects (78.6%) and 3 female subjects (21.4%) were in stage 4, while in stage 5, there were 8 males (57.1%) and 6 females (42.9%). A previous study by Augustine et al. on the relationship between gender and PD stages also found no significant association ($p = 0.463$; OR = 0.709). The nonsignificant findings of this study align with other research that also found no significant link between gender and PD severity [32].

This study presents several notable strengths. First, its applicability in daily medical practice is relatively high. Serum vitamin D level assessment is easily accessible in laboratory settings, involves relatively low cost, and yields results within a short time frame. Therefore, if suboptimal serum vitamin D levels are detected, clinicians can promptly initiate interventions, such as vitamin D supplementation, to help prevent the progression of Parkinson's disease stages. This approach demonstrates considerable practical value in efforts to manage and slow the progression of the disease. Moreover, the analysis revealed a statistically significant association between higher serum vitamin D levels and lower stages of Parkinson's disease. Research exploring this relationship, particularly using the modified Hoehn and Yahr scale, remains limited especially in Asian populations, including Indonesia. Thus, this study contributes meaningfully to the local and regional scientific literature and opens opportunities for further research in this field.

The researcher acknowledges certain unavoidable limitations that may affect the interpretation of this study's findings. One of the main limitations is the reduction in sample size from 74 to 60 participants due to the exclusion of 14 subjects whose blood serum samples were hemolyzed, resulting in extreme vitamin D values. This limitation may restrict the generalizability of the findings to the broader population. A larger sample size and broader sampling scope are needed to enhance statistical accuracy and improve the representativeness of the results.

CONCLUSION

There is a negative relationship between serum vitamin D levels and the stage of Parkinson's disease. Higher serum vitamin D levels are associated with lower stages of Parkinson's disease.

Each one-unit increase in serum vitamin D concentration is linked to a 6.5% reduction in the risk of disease progression.

This study may serve as a foundation for the development of vitamin D–based interventions as part of a multidisciplinary approach to Parkinson's disease management. Routine screening of serum vitamin D levels is recommended for patients with Parkinson's disease. Detection of low vitamin D levels should be followed by supplementation to reduce the risk of disease progression. All patients with Parkinson's disease should also receive comprehensive education on strategies to increase serum vitamin D levels through vitamin D–rich dietary intake and optimal sun exposure. Future research should aim to improve the accuracy and speed of serum sample preparation to minimize the risk of hemolysis. A more in-depth analysis of other potential factors influencing serum vitamin D levels, such as dietary patterns, physical activity, and vitamin D supplementation history, is also warranted. We encourage further studies to involve community-based populations of Parkinson's disease patients in targeted regions to obtain more representative data.

ETHICS APPROVAL STATEMENT

This study was approved by the Ethics Committee of the Faculty of Medicine, Udayana University, with protocol 2476/UN14.2.2.VII.l4/LT/2O24

CONFLICT OF INTEREST

There are no conflicts of interest to declare by any of the authors of this study.

AUTHOR'S CONTRIBUTIONS

Conceptualization, HNA, TIP, and DPGPS; methodology, AAAPL and DKIU; software, HNA and TIP; validation, AARS DPGPS; formal analysis, HNA and TIP; investigation, HNA; resources, HNA; data curation, HNA, AAASIK, SYT, and DPGPS; writing—original draft preparation, HNA and TIP; writing—review and editing, DKIU, AARS, and SYT; visualization, HNA; supervision, AAASIK, DKIU, SYT, DPGPS, and AARS; project administration, HNA. All authors have read and agreed to the published version of the manuscript.

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FIGURES, TABLES AND SCHEMES

Table 1. General characteristic of subjects

Characteristic of Subjects		n (%)
Gender		
Male		37 (61,7)
Female		23 (38,3)
Age (Years) mean ± SD	59 ± 10,476	
Education		
Elementary School		4 (6,7)
Junior High School		8 (13,3)
Senior High School		25 (41,7)
Diploma or Higher		23 (38,3)
Occupation		
Unemployed or Retired		21 (35)
Farmer or Laborers		5 (8,3)
Self Employed		4 (6,7)
Private Employee		15 (25)
Government Employee		15 (25)
Parkinson Disease Staging		
Stage 1		3 (5)
Stage 1,5		7 (11,7)
Stage 2		8 (13,3)
Stage 2,5		4 (6,7)
Stage 3		10 (16,7)
Stage 4		14 (23,3)
Stage 5		14 (23,3)
Duration of Parkinson Disease		
< 1 Year		9 (15)
1- 5 Years		31 (51,7)
> 5 Years		20 (33,3)
Duration of Sunlight Exposure		
< 30 minutes		25 (41,7)
> 30 minutes		35 (58,3)
Vitamin D Serum (ng/ml):		
Median (IQR)	37,5 (29,73)	
Serum Vitamin D Serum (ng/ml):		
Deficiency (≤20)		11 (18,3)
Insuficiency (21-30)		11 (18,3)
Optimal Concentration (>31-80)		38 (63,3)

Table 2 Profile of Parkinson's Disease Patients Based on Serum Vitamin D Levels

Parkinson Disease Staging	Concentration 25(OH)D (ng/ml) n (%)			Gender	
	Deficiency (≤ 20)	Insuficiency (21-30)	Optimal Concentration (31-80)	Male	Female
Stage 1	-	-	3 (100%)	3 (100%)	-
Stage 1,5	-	-	7 (100%)	2 (28,6%)	5 (71,4%)
Stage 2	-	3 (37,5%)	5 (62,5%)	4 (50%)	4 (50%)
Stage 2,5	-	-	4 (100%)	2 (50%)	2 (50%)
Stage 3	-	2 (20%)	8 (80%)	7 (70%)	3 (30%)
Stage 4	3 (21,4%)	4 (28,6%)	7 (50%)	11 (78,6%)	3 (21,4%)
Stage 5	8 (57,1%)	2 (14,3%)	4 (28,6%)	8 (51,7%)	6 (42,9%)

Table 3. Spearman Correlation Analysis of Serum Vitamin D Levels with Age and Duration of Sun Exposure

Variable	Vitamin D Serum (n=60)	
	r	p
Duration of Sunlight Exposure	0,675	0,000*
Age	-309	0,16

Note: * indicates statistical significance if $p < 0.05$

Table 4 Results of Spearman Correlation Analysis Between Parkinson's Disease Stage and Serum Vitamin D Levels

Variable	Parkinson Disease Staging	
	r	p
Vitamin D Serum	-0,589	0,000*

Note: * indicates statistical significance at $p < 0.05$

Table 5. Simple Ordinal Logistic Regression Analysis of Serum Vitamin D on Parkinson's Disease Stage.

Independent Variable	Coefisien Estimate (ß)	OR	CI 95% (lower)	CI 95% (Upper)	*p-value*
Kadar Vitamin D	-0,067	0,935	-0,097	-0,037	0,000*

Note:

*:statistically significant, OR: Odds Ratio; CI: Confidence Interval

Table 6. Simple Ordinal Logistic Regression of Other Variables on Parkinson's Disease Stage

Independent Variable	**Coefficient Estimate (β)**	**Odds Ratio (OR)**	**95% CI (Lower)**	**95% CI (Upper)**	***p*-value**
Age	0.124	1.132	0.07	0.178	0.000*
Gender	-0.344	0.709	-1.264	0.575	0.463
Duration of PD (years)	2.373	10.73	1.493	3.252	0.000*

Note: *:statistically significant, OR: Odds Ratio; CI: Confidence Interval